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Cancer-Related Fatigue and Rehabilitation

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Cancer-Related Fatigue and Rehabilitation: A Randomized Controlled Multicenter Trial Comparing Physical Training Combined With Cognitive-Behavioral Therapy With Physical Training Only and With No Intervention

Ellen van Weert, Anne M. May, Irene Korstjens, Wendy J. Post, Cees P. van der Schans, Bart van den Borne, Ilse Mesters, Wynand J.G. Ros, Josette E.H.M. Hoekstra-Weebers

Background. Research suggests that cancer rehabilitation reduces fatigue in survivors of cancer. To date, it is unclear what type of rehabilitation is most beneficial.

Objective. This randomized controlled trial compared the effect on cancer-related fatigue of physical training combined with cognitive behavioral therapy with physical training alone and with no intervention.

Design. In this multicenter randomized controlled trial, 147 survivors of cancer were randomly assigned to a group that received physical training combined with cognitive-behavioral therapy (PT+CBT group, n=76) or to a group that received physical training alone (PT group, n=71). In addition, a nonintervention control group (WLC group) consisting of 62 survivors of cancer who were on the waiting lists of rehabilitation centers elsewhere was included.

Setting. The study was conducted at 4 rehabilitation centers in the Netherlands.

Patients. All patients were survivors of cancer.

Intervention. Physical training consisting of 2 hours of individual training and group sports took place twice weekly, and cognitive-behavioral therapy took place once weekly for 2 hours.

Measurements. Fatigue was assessed with the Multidimensional Fatigue Inventory before and immediately after intervention (12 weeks after enrollment). The WLC group completed questionnaires at the same time points.

Results. Baseline fatigue did not differ significantly among the 3 groups. Over time, levels of fatigue significantly decreased in all domains in all groups, except in mental fatigue in the WLC group. Analyses of variance of postintervention fatigue showed statistically significant group effects on general fatigue, on physical and mental fatigue, and on reduced activation but not on reduced motivation. Compared with the WLC group, the PT group reported significantly greater decline in 4 domains of fatigue, whereas the PT+CBT group reported significantly greater decline in physical fatigue only. No significant differences in decline in fatigue were found between the PT+CBT and PT groups.

Conclusions. Physical training combined with cognitive-behavioral therapy and physical training alone had significant and beneficial effects on fatigue compared with no intervention. Physical training was equally effective as or more effective than physical training combined with cognitive-behavioral therapy in reducing cancer-related fatigue, suggesting that cognitive-behavioral therapy did not have additional beneficial effects beyond the benefits of physical training.

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Positive Effects of Oncological Rehabilitation on Fatigue

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The number of survivors of cancer is growing due to improvements in diagnosis and treatment of cancer. As a consequence, attention to their quality of life has increased. Over the last 10 years, oncological rehabilitation programs have been developed with the aim of improving quality of life in survivors of cancer who continue to experience physical and emotional problems. The effectiveness of such oncological rehabilitation programs has been reported and seems to vary depending on the content of the program and the target outcome measure. For example, meta-analyses showed weighted effect sizes (ESs) of 0.51 during and 0.65 after cancer treatment for impact of physical training on aerobic capacity, whereas the ESs of similar interventions on quality of life have been estimated at 0.20.^{1–4} Meta-analyses of psychosocial interventions showed ESs varying from 0.31 to 0.36 and 0.42 for quality of life, anxiety, and depression, respectively.^{5–8} Currently, the effect of rehabilitation programs on cancer-related fatigue (CRF) is ambiguous, with ESs found in meta-analyses varying from 0 to 0.23.^{1,3,4,9–11} This variation may be related to the nature of fatigue.

Cancer-related fatigue is one of the most frequently reported complaints in patients with cancer, with a reported prevalence of 70% to 100%.¹² Between 61% and 99% of patients receiving treatment report complaints of fatigue, and 20% to 40% of survivors of cancer who are disease-free experience fatigue years after curative treatment has ended.^{13,14} Fatigue, as a symptom, is a sensation of weakness, lack of energy, or tiredness.¹³ As a syndrome, it has been defined as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work.¹⁵ Cancer-related fatigue is an abstract, multidimensional experience that has a pro-

found effect on the whole person—physically, emotionally, and mentally. Cancer-related fatigue may interfere with normal daily activities and may have devastating social consequences, such as problems in job reintegration or in relationships with others.

Acknowledging the multidimensional construct of CRF, a few studies have reported a beneficial effect of a combined rehabilitation program that included physical training and a psychosocial component.^{16–19} One study revealed that the combination of physical training and psychotherapy resulted in a decrease in fatigue, whereas psychotherapy alone had no effect,²⁰ suggesting that a rehabilitation program at least should include physical exercise.

A recent meta-analysis¹¹ reported that cognitive and behavioral mechanisms such as catastrophic coping and physical inactivity are potential contributors to CRF. Therefore, the authors recommended examining whether an intervention strategy that targets both cognitive and behavioral mechanisms (ie, stress management and exercise training) is more effective than a strategy that targets only one mechanism (ie, exercise training alone).¹¹ To our knowledge, the effect on CRF of physical training alone compared with a combined program of physical exercise and psychotherapy has not been reported in the literature.

For the present study, we acknowledged that CRF is a multidimensional problem including physical and mental components that is present in patients with cancer referred for rehabilitation. The study aimed to determine the effect of a combined rehabilitation program (physical training and cognitive-behavioral training [CBT]) and of physical training alone on CRF in comparison with no intervention. We hypothesized:



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1. Survivors of cancer referred for rehabilitation will report more fatigue than a normative group of the Dutch population both before and after intervention. We expected to still find more fatigue after completion of the intervention because of the long-lasting and severe nature of fatigue in patients with cancer.
2. Both physical training and CBT and physical training alone will have a beneficial effect on fatigue in survivors of cancer, whereas fatigue in survivors of cancer receiving no intervention will not change over time.
3. Survivors of cancer receiving physical training and CBT will report greater reduction in fatigue than survivors of cancer receiving physical training alone, in particular in the psychological domains of fatigue due to the CBT component. We expected to find equally large effects in the intervention groups regarding the physical domains of fatigue.

This study is part of a larger trial comparing the effects of a combined program (physical training and CBT) and physical training alone on quality of life, physical functioning, and CRF. We recently reported significant positive changes in physical fitness, physical activity levels, and quality of life in both intervention groups, but no differences between the intervention groups,²¹⁻²³ indicating no additional beneficial effect of CBT on these outcomes. The effects on CRF may be different because of the nature and complexity of the problem.

Method

Procedure and Setting

Survivors of cancer were informed about the study by leaflets handed out by oncologists and general practitioners, by information in news-

papers, and through a Web site between February 2004 and September 2006. Survivors who expressed interest were sent an information letter, an informed consent form, an intake form, and referral papers. Four centers in the Netherlands experienced in oncological rehabilitation performed the intervention: Erasmus University Medical Center Rotterdam; University Medical Center Groningen; University of Groningen; Hilversum Hospital, Hilversum; and Rehabilitation Center De Hoogstraat, Utrecht.

Participants

Patients were eligible for the study if they met the following criteria: age ≥ 18 years; last cancer-related treatment at least 3 months before study entry; estimated life expectancy of at least 1 year; knowledge of the Dutch language; and a minimum of 3 positive findings, as judged by the physician who referred the patient, for physical complaints, reduced physical capacity, psychological prob-

lems, increased fatigue, sleep disturbances, or problems in coping with reduced physical and psychosocial functioning. Patients were excluded if they: had a very low level of activity (ie, category 3 or 4 according to the classification of Winningham^{*,24}), were unable to travel independently to the rehabilitation center, had cognitive disturbances or serious psychopathology or emotional instability that might impede participation in the rehabilitation program, or were in need of intensive medical treatment or rehabilitation.

Design, Randomization, and Allocation

The study was a randomized controlled multicenter trial. Eligible participants, after providing written in-

* This scheme determines the activity level of patients and ranges from 0 to 4 (0=active, no limitations; 1=ambulatory, decreased leisure activity; 2=ambulatory more than 50% of the time; 3=ambulatory 50% or less of the time; and 4=confined to bed).

The Bottom Line

What do we already know about this topic?

Cancer-related fatigue (CRF) is a multidimensional problem that includes physical and mental components, and is one of the most frequently reported complaints in patients with cancer. The effect on CRF of physical training alone compared with a combined program of physical exercise and psychotherapy has not been reported in the literature.

What new information does this study offer?

Twelve weeks of group or individual physical training and group sports and games were equally effective in reducing fatigue. The combination of physical training and cognitive-behavioral therapy (a psychotherapeutic, systematic, goal-oriented approach aimed at finding solutions to stressful problems and changing dysfunctional cognition, emotions, and behaviors) may be more effective than the traditional exercise-only approach.

If you're a patient, what might these findings mean for you?

Rehabilitation programs aimed at reducing CRF should contain a physical training component such as aerobic and strength exercises.

formed consent, were randomly assigned to a group that received physical training combined with CBT or a group that received physical training alone and were scheduled for baseline measurements. Randomization was conducted at the group level by an independent researcher using a randomization list. Consecutive groups of 8 to 12 patients were randomly assigned to each group. Both interventions were balanced in each center. Until the first session, participants were blinded to the intervention they were allocated to receive. Therapists could not be blinded, as they had to schedule the intervention sessions. Main investigators were not blinded to group assignment. The Multidimensional Fatigue Inventory (MFI) was completed prior to the start of the intervention and immediately following the intervention, and outcome assessors, as well as participants and therapists, were blinded to the MFI scores. A nonintervention control group (WLC group) consisted of patients who were referred for oncological rehabilitation at other Dutch centers that used the same inclusion and exclusion criteria as in the present study and who had to wait to start rehabilitation for at least 3 months. The WLC group filled in questionnaires upon enrollment and 12 weeks later.

Interventions

Both components of the 12-week rehabilitation program (ie, physical training and CBT) were based on the principles of self-management, including goal setting, monitoring, norms and decision making, action, and self-reflection.²⁵ In addition, sources of self-efficacy were enhanced through mastery of experiences and perceived success, modeling, social persuasion, and physiological feedback, in line with Bandura.²⁶ Moreover, attention was paid to the role of irrational illness perceptions in both components because of their

impeding effect on coping and functioning.²⁷ All therapists received a manual and were trained to ensure that the standardized intervention was delivered as intended.

Physical training. Physical training²⁸ consisted in total of 24 hours of individual physical training and 24 hours of group sports and games, each conducted twice a week for 1 hour. The individual physical training was supervised by 2 physical therapists who were experienced in the delivery of physical training interventions to patients with cancer. Individual physical training was preceded by a physical assessment to define patients' problems by assessing peak exercise capacity using symptom-limited bicycle ergometry,²⁹ muscle strength (force-generating capacity),³⁰ and medical history. The medical history included questions on a patient's reduction in exercise capacity, role functioning, and activity pattern. Based on termination of the bicycle ergometry test, muscle strength testing, and medical history, it was established whether and to what extent a patient had decreased aerobic capacity, reduced muscle strength, fatigue, or limited physical role functioning. Consequently, patients chose their individual goal (ie, improving exercise capacity, improving muscle strength, coping with fatigue, or coping with physical role limitations) in collaboration with the physical therapist. In accordance with patients' goals, 4 treatment modules were available. All modules consisted of individual aerobic training (20–30 minutes), muscle strength training (20–30 minutes), and information. Modules slightly differed in increase in training intensity and in the content of information provided. Intensity of the aerobic training was determined based on the maximal heart rate (HR_{max}) reached during symptom-limited ergometry and the Karvonen formulas.^{31,32}

During the first 4 weeks, aerobic training was performed at a training heart rate (HR_{tr}) of $HR_{rest} + 40\% - 50\%$ of $(HR_{max} - HR_{rest})$, where HR_{rest} is resting heart rate. From week 5 onward, the training intensity gradually increased to an HR_{tr} of $HR_{rest} + 50\% - 80\%$ of $(HR_{max} - HR_{rest})$ at week 12, in accordance with training guidelines.³³ The increase in training intensity was based on physiological adjustments (ie, lower heart rate at the same wattage) and Borg scale scores for dyspnea and fatigue (ie, lower perceived fatigue or dyspnea at the same level of exercise). The increase was incremental for patients whose primary goal was to improve exercise capacity and more gradual for patients with other goals. For the first group, increases in the cycling wattage, HR_{tr} , and duration per session were aimed at achieving an HR_{tr} of $HR_{rest} + 80\%$ of $(HR_{max} - HR_{rest})$, if possible, in week 8, and in week 10 for the other groups.

Progressive resistance muscle training of the trunk and the lower and upper extremities was based on the individual 1-repetition maximum (1-RM).³⁴ Progressive resistance muscle training³³ started at 30% of 1-RM and was increased to 60% of 1-RM in week 12 for participants whose primary goal was improvement of aerobic capacity or improvement of muscle strength and to 50% of 1-RM for patients with other goals, indicating that the increase of repetitions, sets, and percentage of 1-RM was higher in the first 2 groups.

All patients received information on the benefits of exercise. Additionally, patients who aimed at coping with fatigue received an illustrative "model of fatigue," and patients who aimed to improve role functioning were taught how to restore the balance between demand and capacity during tasks and activities.

Self-management principles²⁵ were incorporated by asking the patients to set their personal training goals and monitor their own training process using exercise logs, heart rate sport testers, and the Borg scale for dyspnea and fatigue. The actual physical training fulfilled the phase of action. Self-reflection was encouraged by visual and oral feedback, such as graphics on exercise performance combined with reflective questions from the physical therapists. Sources of self-efficacy were systematically addressed as follows. First, in the first weeks of the program, the training intensity was low to ensure that all participants would be able to complete the training and thus perceive a mastery experience that might increase self-efficacy. Second, verbal persuasion was used by the therapist to encourage a patient to perform the training activities. Third, the program was delivered in a group format to enhance vicarious learning. Finally, improvement in exercise capacity was considered to affect physiological arousal that, in turn, might increase self-efficacy. Attention to illness perceptions was addressed; irrational perceptions were explored and challenged by providing information, raising doubt, and suggesting alternative perceptions.

The goal of group sports and games was to encourage a physically active lifestyle. A variety of sports and games, such as badminton, curling, and field hockey were played to stimulate patients to perform and enjoy sports and to increase their level of activity in leisure times. In line with the individual physical training, the group sports and games were based on a self-management approach and self-efficacy enhancement techniques, such as goal setting and acquiring mastery experiences. The group sports and games module had a fixed structure, including warming up, playing the game or sport, and cooling down, which was described in the manual.

More-detailed information on the development and the content of the program has been described elsewhere.²⁸

CBT. Cognitive-behavioral therapy was conducted for a total of 24 hours (once a week, 2 hours per session) and was supervised by 2 psychologists. To enable participants to solve problems associated with psychosocial and physical consequences of cancer, CBT was aimed at training self-management skills based on the cognitive-behavioral problem-solving approach of Nezu et al.³⁵ This psychotherapeutic, systematic, goal-oriented approach is aimed at finding effective and adaptive solutions to stressful problems and at changing dysfunctional cognition, emotions, and behaviors.³⁶ Topics such as distress, exercise physiology, and relaxation were discussed during the first 4 sessions. In sessions 5 to 12, participants primarily were trained to apply self-management skills to realize personal goals by practicing the following steps in the circular problem-solving process: (1) problem orientation, (2) problem definition and formulation and goal setting, (3) generation of alternative solutions (brainstorming), (4) decision making, and (5) solution implementation and verification. The structure of each session consisted of recapitulation of the previous week's session and exchange of everyday life experiences, discussion of the homework assignment, introduction of a new topic or self-management skill, self-management skills practice, introduction of the next homework assignment, and relaxation exercises. Homework assignments (maximally 0.5 hour weekly) and practicing of activities were used to achieve generalization to daily life during and after rehabilitation.

Adherence to intervention and adverse events. To monitor adherence to the intervention and to record adverse events, the exercise trainers and psychologists completed

a case record form for each participant after each session. After each visit, the investigator obtained data about the health of the participants.

Outcome Measures

Fatigue was measured with the MFI, which measures the following 5 dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.³⁷ Every dimension contains 4 items, and answers are given on a 5-point Likert scale, ranging from "yes, that is true" to "no, that is not true." Scores have a range of 4 to 20, and a higher score reflects a greater sense of fatigue. In the present study, Cronbach α values ranged from .73 to .83 in the preintervention assessment and from .84 to .88 in the postintervention assessment. Data for sociodemographic and medical variables were collected from participants, with confirmation of medical data by the referring physicians.

Data Analyses

Statistical analyses were performed using SPSS statistical software, version 16.0.[†] Two-sided significance tests were used ($\alpha < .05$). We used *t* tests and chi-square tests to examine differences in baseline sociodemographic and medical characteristics between included and excluded patients, as well as between participants who completed the study and those who dropped out. Chi-square tests and analyses of variance (ANOVAs) were used to examine differences in sociodemographic and medical characteristics and in baseline fatigue scores among the PT+CBT, PT, and WLC groups.

Confidence interval (CI) analyses were performed to compare patients with a normative group of the Dutch population ($n=139$, mean [SD] age=46 [16] years, 56% female). Ef-

[†] SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.

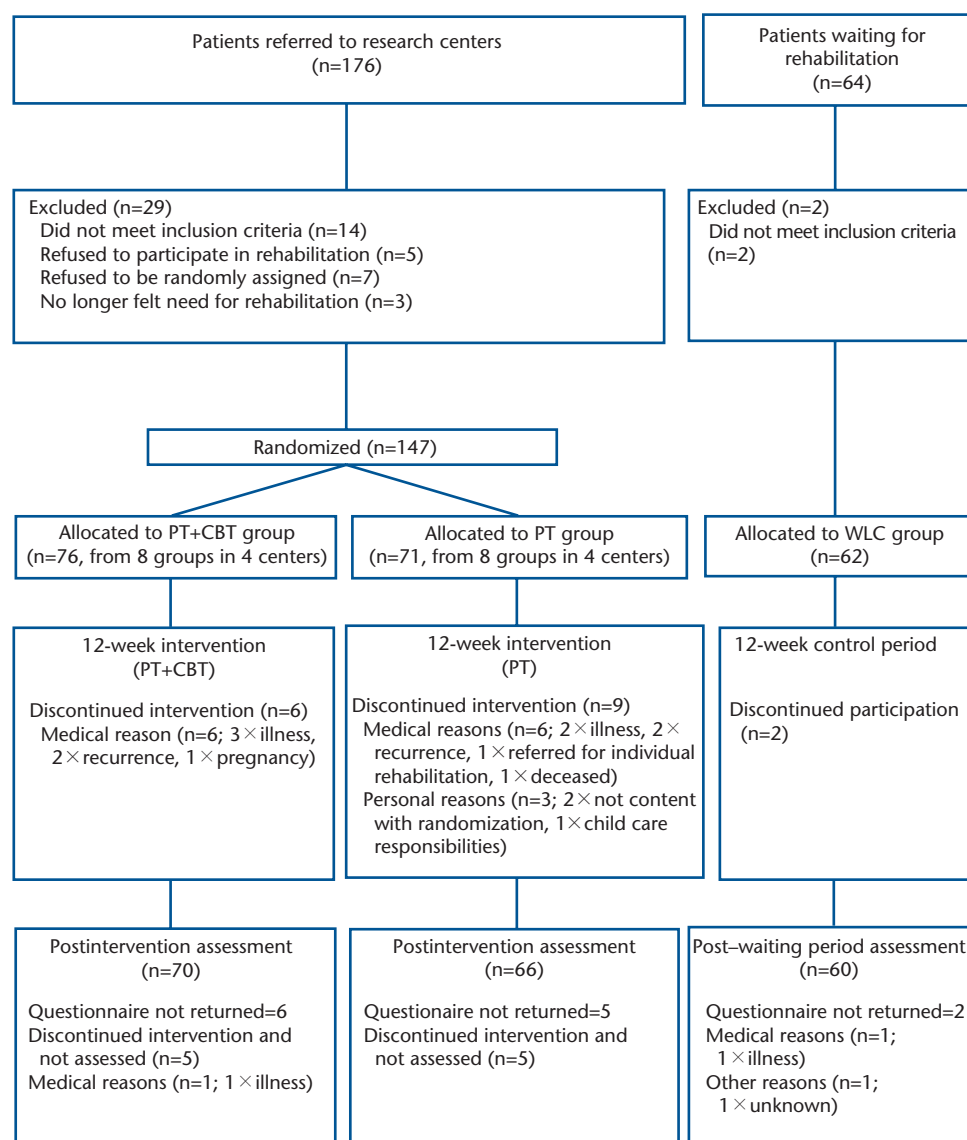


Figure.

Flow chart of the participants, modified with permission.^{21,22} PT+CBT group received physical training combined with cognitive-behavioral therapy, PT group received physical training alone, and WLC group received no intervention.

effect sizes were calculated according to the Cohen *d* statistic.³⁸ An ES of <0.2 reflects a “negligible difference,” an ES of ≥ 0.2 and ≤ 0.5 reflects a “small difference,” an ES of ≥ 0.5 and ≤ 0.8 reflects a “moderate difference,” and an ES of ≥ 0.8 reflects a “large difference.”

We conducted ANOVAs to investigate differences in postintervention fatigue among the PT+CBT, PT, and WLC groups. We corrected for base-

line fatigue and any baseline factors on which the rehabilitation groups and the WLC group differed because patients were not randomized to the WLC group. Variables that had a significant effect on postintervention fatigue were included in the final model only. The Levene test was used to examine equality of error variance. To account for multiple testing, we performed Bonferroni corrections, with adjusted CIs, to investigate differences among

the PT+CBT, PT, and WLC groups and *post hoc* among levels of education.

Results

Patient Characteristics

No differences were found in baseline sociodemographic and medical characteristics between the 209 patients who were included and the 31 patients who were excluded or declined to participate (Figure), except that excluded or declining

Table 1.
Patients' Characteristics and Comparisons Among Groups^a

| Variable | PT+CBT Group (n=76) | PT Group (n=71) | WLC Group (n=62) | <i>P</i> ^b |
|--|------------------------|--------------------|---------------------|-----------------------|
| Age (y), mean (SD) | 47.8 (10.5) | 49.9 (11.3) | 51.3 (8.8) | .13 |
| Sex, n (%) | | | | |
| Male | 10 (13.2) | 14 (19.7) | 6 (9.7) | .24 |
| Female | 66 (86.8) | 57 (80.3) | 56 (90.3) | |
| Married/living together, n (%) | 53 (69.7) | 51 (71.8) | 55 (88.7) | .02 |
| Educational level, n (%) | | | | |
| Low | 6 (7.9) | 14 (19.7) | 16 (25.8) | .04 |
| Medium | 40 (52.6) | 32 (45.1) | 32 (51.6) | |
| High | 30 (39.6) | 25 (35.2) | 14 (22.6) | |
| Employment status at baseline, n (%) | | | | |
| Employed | 32 (42.1) | 23 (32.4) | 24 (38.7) | .47 |
| Not employed | 44 (57.9) | 48 (67.6) | 38 (61.3) | |
| Type of cancer, n (%) | | | | |
| Breast | 48 (63.2) | 34 (47.9) | 38 (61.3) | .053 |
| Hematological | 15 (19.7) | 8 (11.3) | 10 (16.1) | |
| Gynecological | 6 (7.9) | 11 (15.5) | 7 (11.3) | |
| Other | 7 (9.2) | 18 (25.4) | 7 (11.3) | |
| Type of treatment >3 months before enrollment, n (%) | | | | |
| Surgery | 64 (84.2) | 62 (87.3) | 51 (83.3) | .50 |
| Radiation | 43 (56.6) | 41 (57.7) | 39 (62.9) | |
| Chemotherapy | 55 (72.2) | 45 (63.4) | 41 (66.1) | |
| Cancer recurrence >3 months before enrollment, n (%) | | | | |
| Yes | 7 (9.2) | 7 (9.9) | 15 (24.2) | .03 |
| No | 66 (86.8) | 63 (88.7) | 47 (75.8) | |
| Unknown | 3 (3.9) | 1 (1.4) | 0 (0) | |
| Time posttreatment (y), mean (SD) | 1.2 (1.3) | 1.4 (2.1) | 1.9 (2.7) | .15 |
| Comorbidity, n (%) | | | | |
| Yes | 36 (52.6) | 32 (45.1) | 27 (43.5) | .92 |
| No | 40 (47.4) | 39 (54.9) | 34 (54.8) | |
| Missing | | | 1 (1.6) | |

^a PT+CBT group received physical training combined with cognitive-behavioral therapy, PT group received physical training alone, and WLC group received no intervention.

^b *P* values for comparisons among groups based on chi-square analyses and analysis of variance tests.

participants received radiotherapy significantly more often compared with included participants (77.4% versus 58.9%, $P<.05$). Participants who completed the study more often reported having comorbidity compared with those who dropped out (47.7% versus 15.4%, $P<.05$). No differences in fatigue at baseline were found between those

who completed the study and those who dropped out.

Participants in the 3 groups did not differ in age, sex, type of cancer, type of treatment, comorbidity, or time since completion of treatment. However, compared with the patients in the intervention groups, the WLC group participants' educational

level was significantly lower ($P=.04$), they were more often married or cohabiting ($P=.02$), and more of them had had a cancer recurrence >3 months before rehabilitation ($P=.03$) (Tab. 1). The ANOVAs revealed no significant differences in fatigue among the 3 groups at baseline.

Positive Effects of Oncological Rehabilitation on Fatigue

Table 2.

Comparison Between General Population and Patients at Baseline and Postintervention Based on Confidence Interval (CI) Analyses, Within-Group Changes (Preintervention to Postintervention) Based on Paired *t* Tests, and Effect Sizes According Cohen³⁸

| Domain | Dutch Population, Mean (SD) | Group ^a | Preintervention, Mean (SD) | Postintervention, Mean (SD) | Within-Group Change Scores (95% CI) | Effect Size |
|--------------------|-----------------------------|--------------------|----------------------------|-----------------------------|-------------------------------------|-------------|
| General fatigue | 9.91 (5.2) | PT+CBT | 15.7 (3.5) ^b | 11.4 (3.3) ^c | -4.3 (-5.3 to -3.4) ^d | -1.26 |
| | | PT | 15.6 (3.3) ^b | 11.6 (3.8) ^c | -4.0 (-4.9 to -3.1) ^d | -1.05 |
| | | WLC | 15.1 (3.3) ^b | 13.1 (4.1) ^e | -2.0 (-2.9 to -1.0) ^d | -0.56 |
| Physical fatigue | 9.79 (4.9) | PT+CBT | 15.6 (3.3) ^b | 9.3 (3.5) | -6.3 (-7.3 to -5.4) ^d | -1.79 |
| | | PT | 15.0 (3.3) ^b | 10.1 (3.7) | -4.9 (-5.8 to -4.0) ^d | -1.36 |
| | | WLC | 14.3 (3.7) ^b | 12.3 (4.3) ^e | -2.0 (-2.9 to -1.1) ^d | -0.50 |
| Mental fatigue | 8.69 (4.6) | PT+CBT | 13.3 (3.8) ^b | 11.4 (3.6) ^f | -1.9 (-2.8 to -1.1) ^d | -0.52 |
| | | PT | 12.7 (4.5) ^b | 10.5 (3.8) ^f | -2.2 (-3.1 to -1.2) ^d | -0.47 |
| | | WLC | 12.8 (4.4) ^b | 11.9 (4.4) ^f | -0.9 (-2.1 to 0.2) | -0.18 |
| Reduced motivation | 8.23 (4.0) | PT+CBT | 10.7 (3.4) ^b | 8.1 (3.6) | -2.6 (-3.4 to -1.8) ^d | -0.76 |
| | | PT | 10.7 (4.3) ^b | 8.2 (3.5) | -2.4 (-3.3 to -1.4) ^d | -0.67 |
| | | WLC | 11.4 (3.7) ^b | 10.0 (3.7) ^f | -1.4 (-2.1 to -0.7) ^d | -0.38 |
| Reduced activation | 8.3 (4.8) | PT+CBT | 13.2 (4.2) ^b | 9.4 (4.0) | -3.8 (-4.7 to -2.9) ^d | -0.97 |
| | | PT | 12.7 (3.7) ^b | 9.2 (3.4) | -3.5 (-4.4 to -2.5) ^d | -0.98 |
| | | WLC | 13.1 (3.9) ^b | 11.1 (4.3) ^e | -2.0 (-2.9 to -1.1) ^d | -0.34 |

^a PT+CBT group received physical training combined with cognitive-behavioral therapy, PT group received physical training alone, and WLC group received no intervention.

^b $P < .001$ for CI analyses between patients preintervention and the Dutch population.

^c $P < .05$ for CI analyses between patients postintervention and the Dutch population.

^d $P < .001$ for within-group changes (preintervention to postintervention).

^e $P < .001$ for CI analyses between patients postintervention and the Dutch population.

^f $P < .01$ for CI analyses between patients postintervention and the Dutch population.

Adherence and Adverse Events

Patients in the PT+CBT group completed 82.4% of 12 CBT sessions (mean [SD]=9.9 [2.4]) and 83.5% of 24 physical training sessions (mean [SD]=20 [4.7]). Patients in the PT group completed 83.5% of 24 physical training sessions (mean [SD]=20 [5.2]).

One participant in the PT group collapsed at the start of a training session during low-intensity warm-up and died at the first-aid station. An autopsy showed that death was caused by cardiac arrest resulting from a hemorrhage from a residual carcinoma in the participant's left primary bronchi. The physicians judged that the death was not related to the exercise program. No further adverse events were reported.

Patients' Fatigue in Comparisons With the Normative Reference Group (Hypothesis 1)

At the preintervention assessment, CI analyses showed that patients in the PT+CBT, PT, and WLC groups had significantly higher fatigue scores compared with the normative Dutch population in all fatigue domains. At the postintervention assessment, the WLC group reported statistically significantly more fatigue in all domains; the PT+CBT and PT groups reported more general and mental fatigue compared with the normative Dutch population (Tab. 2).

Effects of Rehabilitation on Fatigue, Time, and Group Effect (Hypotheses 2 and 3)

Over time, reported levels of fatigue significantly decreased in all domains

in all groups, except in mental fatigue in the WLC group. Effect sizes were moderate to large in the intervention groups and ranged from negligible to moderate in the WLC group (Tab. 2). Analyses of variance, corrected for preintervention fatigue and adjusted for educational level, marital status, and cancer recurrence, showed an overall statistically significant effect of group on 4 domains of postintervention fatigue: general fatigue ($P=.007$), physical fatigue ($P<.001$), mental fatigue ($P=.04$), and reduced activation ($P=.02$). The effect on reduced motivation just failed to reach significance ($P=.065$). Preintervention fatigue significantly affected postintervention fatigue (Tab. 3).

In comparison with the WLC group, the PT group reported significantly greater reduction in general fatigue, physical fatigue, mental fatigue (for patients with a low educational level), and reduced motivation. In comparison with the WLC group, the PT+CBT group reported significantly greater reduction in physical fatigue only. No significant differences in reduction in fatigue were found between the PT+CBT and PT groups (Tab. 4).

Post Hoc Analyses

Educational level had a significant effect on postintervention physical fatigue, reduced motivation, and reduced activation (Tab. 3). Subsequent Bonferroni analyses showed that patients with a low educational level reported less decline in postintervention physical fatigue ($P=.05$), reduced motivation ($P=.01$), and reduced activation ($P=.05$) compared with patients with a medium educational level. Patients with a low educational level reported less decline in reduced motivation ($P=.008$) and reduced activation ($P=.01$) after intervention compared with patients with a high educational level. Patients with a low educational level tended to report less reduction in general fatigue ($P=.053$) postintervention compared with patients with a medium educational level, and they also tended to report less reduction in postintervention physical fatigue ($P=.07$) compared with patients with a high educational level. Marital status and cancer recurrence >3 months before rehabilitation had no effect on postintervention fatigue.

The majority of the participants chose to improve aerobic capacity (35%) or cope with role limitations (45%), and a minority chose to improve muscle strength (10%) or cope with fatigue (8%) (13%=missing). Due to this skewed distribution and the consequent lack of power, we

Table 3.

Analysis of Variance Tests on Fatigue Postintervention Corrected for Preintervention Fatigue and Adjusted for Educational Level

| Domain | F | P ^a |
|-------------------------|-------|----------------|
| General fatigue | | |
| Fatigue preintervention | 40.21 | <.001 |
| Condition | 5.04 | .007 |
| Education | 3.00 | .052 |
| Physical fatigue | | |
| Fatigue preintervention | 52.14 | <.001 |
| Condition | 9.83 | <.001 |
| Education | 3.20 | .04 |
| Mental fatigue | | |
| Fatigue preintervention | 64.63 | <.001 |
| Condition | 3.26 | .04 |
| Education | 0.38 | .68 |
| Reduced motivation | | |
| Fatigue preintervention | 78.01 | <.001 |
| Condition | 2.78 | .065 |
| Education | 2.77 | .007 |
| Reduced activation | | |
| Fatigue preintervention | 84.62 | <.001 |
| Condition | 3.9 | .02 |
| Education | 2.47 | .02 |

^a P values for comparisons among groups based on analysis of variance tests.

were not able to analyze differences in fatigue outcomes across subgroups of participants according to training goal preference.

Discussion

The results of this study showed that survivors of cancer at the time of referral to rehabilitation reported more fatigue compared with a Dutch reference population. At the postintervention assessment, levels of fatigue had decreased in both intervention groups in all domains. However, fatigue scores were still higher in 2 of the 5 fatigue domains in the PT and PT+CBT groups compared with the Dutch reference population. The WLC group reported higher fatigue scores in all domains compared with the normative Dutch population at 3 months after referral, although their fatigue had decreased

over time in 4 domains without oncological rehabilitation. In comparison with the WLC group, the PT group showed more reduction in 4 domains of fatigue, whereas the PT+CBT group showed more reduction in one domain only. Finally, the results showed that physical training combined with CBT and physical training alone were equally effective in reducing fatigue. Thus, CBT did not seem to contribute additional positive effects on fatigue to the benefits of physical training.

The hypothesis that patients referred for rehabilitation would report more fatigue compared with a normative group of the Dutch population both at baseline and postintervention was partly confirmed. In support of our hypothesis, we found that survivors of cancer showed higher fatigue

Table 4.

Between-Group Changes (95% Confidence Interval [CI]) With Waiting List Control and Physical Training Conditions as Reference, Based on Analysis of Variance Tests on Fatigue Postintervention Corrected for Preintervention Fatigue and Adjusted for Educational Level

| Domain | Condition ^a | Between-Group Change (95% CI) ^b (WLC=Reference) | Between-Group Change (95% CI) ^b (PT=Reference) |
|--------------------|------------------------|--|---|
| General fatigue | PT+CBT | -1.3 (-3.1 to 0.4) | 0.6 (-1.1 to 2.3) |
| | PT | -2.0 (-3.5 to -0.5) ^c | Reference |
| | WLC | Reference | |
| Physical fatigue | PT+CBT | -2.7 (-4.5 to -1.0) ^c | -0.3 (-2.0 to 1.4) |
| | PT | -2.4 (-4.0 to -0.9) ^d | Reference |
| | WLC | Reference | |
| Mental fatigue | PT+CBT | -0.5 (-2.3 to 1.2) | 1.0 (-0.7 to 2.8) |
| | PT | -1.6 (-3.1 to -0.1) ^e | Reference |
| | WLC | Reference | |
| Reduced motivation | PT+CBT | -0.6 (-2.1 to 1.0) | 0.7 (-0.8 to 2.2) |
| | PT | -1.3 (-2.6 to 0.36) | Reference |
| | WLC | Reference | |
| Reduced activation | PT+CBT | -0.9 (-2.6 to 0.8) | 0.8 (-0.9 to 2.4) |
| | PT | -1.7 (-3.1 to -0.2) ^e | Reference |
| | WLC | Reference | |

^a CBT=cognitive behavioral therapy (n=70), PT=physical training (n=66), WLC=waiting list control (n=60).

^b Between-group change scores and corresponding 95% CI and *P* values based on analysis of variance tests and Bonferroni analyses.

^c *P*<.01.

^d *P*<.001.

^e *P*<.05.

scores at the preintervention assessment compared with the Dutch normative population. One of the 6 referral criteria for rehabilitation was increased fatigue. It seems that patients included in the study met this criterion and indeed belonged to the target population for this rehabilitation program. Based on the persistent and severe nature of fatigue in patients with cancer, we expected to still find more fatigue after completion of the intervention. In contrast to our expectations, we found that survivors of cancer who received oncological rehabilitation reported levels of fatigue in 3 domains (ie, physical fatigue, reduced motivation, and reduced activation) that were comparable to the Dutch comparison group, suggesting that the intervention was more powerful in

reducing fatigue than expected. Although CRF may be distinctly different from fatigue in individuals who are healthy, as CRF is not necessarily alleviated by rest and sleep and its symptoms are disproportionate to a person's level of actual physical exertion,³⁹ the results of the present study may indicate a normalization of the nature and intensity of fatigue.

The hypothesis that physical training combined with CBT and physical training alone would have a beneficial effect on fatigue, whereas patients receiving no intervention would show no change over time, was partially confirmed. As expected, we found a decline over time, in fatigue in all domains in both intervention groups. Surprisingly, the participants in the WLC group, who did not re-

ceive oncological rehabilitation, also reported a decline in 4 of the 5 domains of fatigue. However, they continued to have higher scores compared with the normative population in all fatigue domains at 3 months. In addition, ESs in the intervention groups were moderate to large, indicating clinically relevant effects, whereas ESs in the WLC group ranged from negligible to moderate. One explanation for the decline in fatigue found in the WLC group may be natural recovery or maturation over time. Another explanation may be that the survivors of cancer in the WLC group knew they were going to receive a supportive intervention in the near future and that this knowledge generated hope and reassurance causing an unintentional decrease in fatigue. Like the intervention groups, the WLC group had a physical assessment (ie, symptom-limited bicycle ergometry), which might have induced feelings of safety to engage in physical exercise at home, leading to an increase in physical activities and, therefore, less fatigue. The participants were free to engage in physical activity and psychological counseling during their period of waiting. We did not take these possible effects into account in our study. Lastly, it cannot entirely be ruled out that the effects of the interventions might have been due to attention that was given to the patients in the intervention groups, as the WLC group was not given a placebo intervention, but instead received nothing. Future research might include a placebo group to overcome these problems.

The hypothesis that patients in the PT+CBT group would show greater reduction in fatigue compared with patients in the PT group, in particular in the more psychological domains such as mental fatigue and reduced motivation, was not confirmed. We expected that the multidimensional nature of the physical training combined with CBT intervention would induce more benefi-

cial effects than physical training alone based on the multidimensional problem of CRF, which includes physical and mental components. However, no significant differences in decline in fatigue were found between the PT+CBT and PT groups. In comparison with the WLC group, the PT group reported a significantly greater decline in 4 domains of fatigue, whereas the PT+CBT group experienced significantly greater decline in physical fatigue only. This finding indicates that CBT had no additional effects beyond that of physical training alone. Apparently, our physical training, which included aerobic exercise, progressive muscle strength training, and sports, had beneficial effects on CRF. This finding is in line with recent studies that showed beneficial effects of aerobic training *combined* with progressive resistance exercise on CRF.^{40–42} Combining aerobic and resistance exercise seems to produce better results³⁹ (ie, more and rapid effects on CRF) compared with aerobic exercise alone, considering the lower ESs reported in meta-analyses of earlier studies.^{1,3,4,9–11}

An explanation for the finding that CBT had no additional effect may be that our physical training intervention was not physical training only. As extensively described elsewhere,²⁸ the physical training components of aerobic exercise, progressive muscle training, and sports were embedded in a self-management approach.²⁵ In addition, self-efficacy-enhancing techniques²⁶ such as mastery performance, verbal persuasion, and modeling were applied, as well as attention to irrational illness perceptions.²⁷ If the mechanism underlying improvement in self-reported fatigue is primarily psychosocial rather than physical, it might be through the similar social and behavioral instruction as part of the self-management approach that CBT had no additional effects beyond those of physical training,

despite the problem-solving exercises during the CBT and home assignments. In addition, the attention given to goal setting, illness perceptions, and strategies to enhance self-efficacy in the PT group may have resulted in less contrast between the study arms. Another explanation for the lack of an additional effect of CBT might be that CBT was not focused on fatigue. The CBT in our study consisted of problem solving in general, and patients could have a variety of problems not necessarily associated with fatigue. A recent Cochrane review on the effectiveness of psychosocial interventions on CRF supports this notion.⁴³ The authors reported that psychosocial interventions specifically tailored to fatigue seem more beneficial than interventions that are not specific.⁴³ A further alternative explanation for the lack of a further decline in fatigue scores when CBT was added to physical training might be that physical training fully optimized fatigue scores. Because we did not include a group that received CBT only in our study, we could not exclude the presence of a ceiling effect on fatigue.

The present study revealed a significant effect of education on the reduction of fatigue in several domains, indicating that patients with a low educational level reported less reduction in fatigue than those with medium or higher educational levels. This finding suggests that patients with medium and high levels of education benefit more from rehabilitation than patients with a low level of education.

Two fifths of the patients chose to improve aerobic capacity, and two fifths chose to cope with role limitations. Ten percent or fewer chose to either improve muscle strength or cope with fatigue. Due to this skewed distribution and the consequent lack of power, we were not able to examine differences in fatigue outcomes across subgroups of

participants according to training goal preference. An explanation for the skewed distribution might be that the choice between the goals was not distinct or that the main goals for most patients were to improve exercise capacity and cope with role limitations. In future research, it would be interesting to assess the motivation for the choices and to examine whether tailored physical training programs can have different effects on fatigue.

With respect to the WLC group, it should be emphasized that these patients were the target population for rehabilitation because they continued to experience cancer-related physical and psychological problems, which were confirmed by a physician. Unfortunately, in the Netherlands, patients in need of rehabilitation, but not in need of acute care, may have to wait for rehabilitation due to limited delivery capacity. Due to financial reasons and limited availability of personnel, rehabilitation centers offer a group rehabilitation program only a few times a year. In most centers, the maximum waiting period is 3 to 4 months.

Strengths, Limitations, and Generalizability

Strengths of the present study were the randomized controlled design; supervised, standardized, and theory-based interventions; large sample size; intention-to-treat analyses; high attendance; and low dropout rates. A limitation of our study was that participants could not be randomly assigned to a waiting list comparison condition. Nevertheless, the groups were well balanced in baseline fatigue scores, and we statistically corrected for any differences in sociodemographic and medical variables. Patients who did not return their questionnaires after the intervention were not included in our analyses. However, the percentage of patients who did not complete the study was

very low (<6%). Moreover, it is not likely that the dropouts were the patients with the worst symptoms of CRF because their levels of fatigue were not different and their comorbidity was lower than that of those who completed the study. Another limitation of our study was that we did not include a group of patients who received CBT only, which could provide insight into the presence of a ceiling effect on fatigue. Due to an overrepresentation of patients with breast cancer, the results cannot be generalized to the entire cancer population.

Clinical Implications and Future Research

The results of the study suggest that rehabilitation programs aimed at reducing CRF should contain a physical training component. Furthermore, the present study focused on a physical training approach that was guided from a self-management perspective. Future research should investigate whether this approach is more effective than the traditional delivery approach (ie, exercise prescription only).

The study supported the effectiveness of physical training in patients with cancer. However, it would be interesting to know whether the effects are sustained over time, indicating the need for long-term follow-up. In addition, the effects of the program might be sustained or enhanced if patients continue to perform physical activities after supervised rehabilitation. By continuing to engage in physical activities and maintaining their level of fitness, patients may have an effective tool to manage their fatigue. That is, it might be beneficial if patients with cancer adopt a physically active lifestyle. Future research, therefore, should investigate the effectiveness of techniques that have the potential to affect such lifestyle changes.

Conclusion

Our study was the first to compare a cancer rehabilitation program consisting of CBT combined with physical training with a program of physical training alone and with no intervention. Physical training alone and physical training combined with CBT had significant, clinically relevant, and more beneficial effects on fatigue compared with no intervention. Physical training was equally effective as—or effective to a broader extent than—physical training combined with CBT in reducing fatigue, suggesting that CBT does not have additional beneficial effects beyond the benefits of supervised physical training.

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